II. REMARKS

Formal Matters

Claims 1-21 and 23 are pending after entry of the amendments set forth herein.

Claims 1-21 and 23 were examined. Claims 1-4, 6-8, 10, 12-21, and 23 were rejected.

Claim 15 is amended. The amendment to claim 15 was made solely in the interest of expediting prosecution, and is not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendment to claim 15 is found throughout the specification, in particular at the following exemplary locations: claim 13 as originally filed; and in the Examples. Accordingly, no new matter is added by this amendment.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Withdrawn rejection

Applicants note with gratitude that the rejection of claims 1, 12, 22, and 23 under 35 U.S.C.§102(b) over Hoshino et al. (EP 0955363) has been withdrawn.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Fronda, Examiner Achutamurthy, and Examiner Deborah Reynolds for the courtesy of an in-person interview which took place on September 19, 2005, which was attended by Examiner Fronda, Examiner Achutamurthy, Examiner Deborah Reynolds, Dr. Jack Newman, Dr. Neil Renninger, and Applicants' representative Paula A. Borden.

During the interview, the written description rejection of claims 1-4, 6-8, 10, 12-21, and 23 under 35 U.S.C.§ 112, first paragraph; the "new matter" rejection of claim 15 under 35 U.S.C.§112, first paragraph; and the rejection of claims 1-4, 6-8, 10, 12-21, and 23 under 35 U.S.C.§103(a) were discussed.

The present response presents arguments made, and amendments proposed, during the interview.

Claims 5, 9, and 11

Applicants note for the record that claims 5, 9, and 11 were not rejected in the instant Office Action. Applicants presume that these claims, if re-written in independent form, would be considered allowable.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-4, 6-8, 10, 12-21, and 23 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 15 was rejected under 35 U.S.C.§112, first paragraph, as allegedly reciting new matter.

These rejections are addressed below in detail.

Claims 1-4, 6-8, 10, 12-21, and 23; written description

The Office Action stated that the claims are "genus claims that are highly variant and encompass many heterologous nucleic acids with widely differing structural, chemical, biological, and physical characteristics which encode many heterologous enzymes in the mevalonate pathway . . .".[1] Applicants respectfully traverse the rejection.

As discussed during the September 19, 2005 in-person interview, the instant claims meet the written description requirement of 35 U.S.C.§112, first paragraph. The written description requirement does not establish a *per se* rule requiring nucleotide-by-nucleotide re-analysis when nucleotide sequences were already known, or readily determined by known procedures. A recent Federal Circuit decision supports Applicants' position.[2]

The instant claims are drawn to methods for synthesizing IPP, and are not drawn to nucleic acids.

The Office Action stated that Applicants have failed to sufficiently describe the claimed invention, such that a skilled artisan would recognize that Applicants "were in possession of the claimed genus of heterologous nucleic acids encoding enzymes in mevalonate pathway, isopentenyl

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[1] Office Action mailed July 28, 2005, page 3.

[2] *Capon v. Eshar,* (Fed. Cir. No. 03-1480, August 12, 2005); available at http://fedcir.gov/opinions/03-1480.pdf; 2005 U.S. App. LEXIS 16865 (Fed. Cir. 2005) (copy attached as Exhibit 1).

pyrophosphate isomerase enzymes, and any isoprenoid-forming enzymes."[3] However, the Office Action fails to take note that the instant claims are *method* claims, and are not directed to compositions encompassing a genus of compounds. The claimed methods are also *not* methods for cloning or isolating mevalonate pathway synthesis genes, but instead are methods *for making IPP*.

The Office Action acknowledged that many nucleic acids encoding mevalonate pathway enzymes were known as of the priority date of the instant application, and indeed were known to be functionally interchangeable from one host to another.

The Office Action's reliance on Lilly is misplaced.

In support of the rejection, the Office Action cited Federal Register 66, No. 4, January 5, 2001 (the "Written Description Guidelines"). The Written Description Guidelines are based in part on *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir.1997) ("*Lilly*"). In particular, the Office Action cites *Lilly* for the proposition that "a chemical compound's name does not necessarily convey a written description of the named chemical compound, *particularly when a genus of compounds is claimed.*"[4] [emphasis added.] Applicants respectfully submit that the Office Action has improperly applied the Written Description Guidelines and *Lilly*.

First, the instant claims are <u>not</u> drawn to a genus of compounds. Instead, the claims are directed to a *method* in which host cells comprising nucleic acids encoding enzymes having the recited activity for a particular step can be used.

Second, in *Lilly*, the claims were directed to a vertebrate cDNA encoding insulin. The inventors in *Lilly* were the first to describe any such insulin-encoding cDNA. The inventors provides a single example of the claimed cDNA -- a rat cDNA encoding insulin. In contrast, the applicants of the instant application have established, and the Office Action agrees, that many nucleic acids encoding mevalonate pathway enzymes <u>were known as of the priority date of the instant application</u>, and furthermore <u>many were known to be functionally interchangeable</u>. As stated in the MPEP at, e.g., §2163 (II)(A)(3)(a), what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[5]

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[3] Office Action, page 4.

[4] Office Action, page 3.

[5] *In re Buchner* 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 231 USPQ 81, 94 (Fed. Cir. 1986); and *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.* 221 USPQ 481, 489 (Fed. Cir. 1984).

The Federal Circuit's decision in Capon is relevant to the instant claims.

The Federal Circuit's decision in *Capon v. Eshhar* (Fed. Cir. No. 03-1480, August 12, 2005; "*Capon*") (Exhibit 1) is relevant to the instant case. *Capon* involved an interference between two parties claiming a chimeric DNA encoding a chimeric single-chain antibody. The parties argued that there was no need to know the structure of the DNA segments to make the claimed chimeric DNAs, because the structure of these components were already known, and methods for identifying, obtaining, and linking DNA segments were known. Despite this showing, the Board of Patent Appeals and Interferences (the "Board") found that neither party's specification met the written description requirement of 35 U.S.C.§112, first paragraph. The Board stated that:

> Their specifications do not satisfy the written description requirement because persons having ordinary skill in the art would not have been able to visualize and recognize the identity of the claimed genetic materials without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results.[6]

The Federal Circuit reversed, finding that the Board "erred in refusing to consider the state of the scientific knowledge".[7] The court in *Capon* stated:

> The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh.[8]

and

> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution... The chimeric genes here at issue are prepared from known

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[6] *Capon* at page 9 (citing Board opinion).

[7] *Capon* at page 14.

[8] *Capon* at page 15.

> DNA sequences of known function....The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.[9]

The instant Office Action raises issues similar to those raised by the Board and addressed by the Federal Circuit in *Capon*. The claimed invention encompasses use of materials that were available in the art -- various nucleic acids encoding mevalonate pathway enzymes -- to produce genetically modified host cells using *known* methods. The claimed invention is directed to a method of producing IPP using these genetically modified host cells. Accordingly, as in *Capon*, the Office should find that applicants' specification fulfills the written description requirement under §112, first paragraph with respect to the claimed invention.

The Office Action asserts that "[r]eciting the biological sources of the enzymes in the claims does not disclose any structural feature and nucleotide sequence common to the genus of enzymes that catalyze the recited reactions."[10] The Office Action also states that "the specification and the art do not disclose any common structural feature and nucleotide sequence that is shared between members of the claimed genus."[11] However, as established by the court in *Capon*, where the level of skill in the art is such that the claimed invention involves the use of known genes of known function, the written description requirement does not require determining this information "afresh". If an enzyme from a known source has been characterized biochemically such that its catalytic activities are known, and even more so if the gene encoding it has been sequenced, then reciting its enzymatic function, as has been done in the instant specification, is sufficient under the law.

The instant specification describes an adequate number of nucleic acids encoding mevalonate pathway enzymes; nucleic acids comprising nucleotide sequences encoding mevalonate pathway enzymes from various organisms were known in the art as of the filing date of the instant application; and such known nucleic acids were known to be functionally interchangeable in mevalonate-producing organisms and/or to retain enzymatic function in non-mevalonate-producing organisms.[12]

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[9] *Capon* at page 15.

[10] Office Action, page 4.

[11] Office Action, page 4.

[12] See detailed discussion in the amendment, filed on February 9, 2005 and responsive to the September 9, 2004 Office

In *Capon*, the Federal Circuit noted that in *Lilly*, which involved claims to a vertebrate cDNA encoding insulin, the cDNA for human insulin *had never been characterized.* This was not the case in *Capon*, in which there was ample information available in the art. Just as in *Capon*, the present invention does ***not*** involve the situation in *Lilly*, which involved claims to a novel gene. In short, the *Lilly* decision simply does not apply to the instant case. Instead, the facts of *Capon* are more similar to those of the instant case. Accordingly, the Office should find, as did the Federal Circuit in *Capon*, that the specification satisfies the written description requirement of 35 U.S.C.§112, first paragraph for the claimed invention.

Claim 15; new matter objection

The Office Action rejected Claim 15 as allegedly reciting new matter in the limitation "further comprising reacting the polyprenyl pyrophosphate isoprenoid precursor in the presence of an isoprenoid-forming enzyme." Applicants respectfully request reconsideration and withdrawal of this rejection. The phrase "polyprenyl pyrophosphate isoprenoid precursor" finds support at several places in the specification and is present in Claim 13, not subject to the rejection. Paragraphs 0076-0078 make clear that such compounds can be used to form various useful isoprenoids (see, e.g., the first sentence of paragraph 0077). Example 5, at paragraph 0106, states that the desired isoprenoid can be formed by employing "additional operons" and then illustrates the use of the *ispA* operon that encodes a farnesyl pyrophosphate synthase enzyme in the process of Claim 15. For these reasons, the Applicants respectfully request reconsideration and withdrawal of the rejection of Claim 15 as allegedly introducing new matter.

Nevertheless, and solely in the interest of expediting prosecution, claim 15 is amended to recite "wherein the isopentenyl pyrophosphate is further modified to provide an isoprenoid." Support for such an amendment is found in claim 13 as originally filed; and in the Examples. Accordingly, no new matter is added.

Action.

Conclusion as to the rejections under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1-4, 6-8, 10, 12-21, and 23 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C.§103(a)

Claims 1, 3, 4, 6-8, 10, 12-14, and 23 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Takagi et al. ((2000) *J. Bacteriol.* 182:4153-4157; "Takagi") in view of Wang et al. (GenBank Accession No. AF119715; "Wang"). Claim 2 was rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Takagi in view of Wang and further in view of Balbas et al. ((1996) *Gene* 172:65-69; "Balbas"). Claims 15-21 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Tagaki in view of Wang and further in view of Fujisaki et al. ((1986) *J. Biochem.* 99:1327-1337; "Fujisaki").

During the September 19, 2005 in-person interview, it was explained that Takagi does not disclose or suggest the subject method as claimed, because the instant claims require that the mevalonate pathway include a step of condensing two molecules of acetyl-CoA to form acetoacetyl-CoA; and the mevalonate pathway discussed in Takagi does not involve such a step.

Claims 1, 3, 4, 6-8, 10, 12-14, and 23 over Takagi in view of Wang

The Office Action stated that: 1) Takagi teaches a method comprising the steps of culturing a transformed *E. coli* strain harboring a gene cluster encoding mevalonate kinase, diphosphomevalonate decarboxylase, phosphomevalonate kinase, and HMG-CoA synthase; 2) Takagi does not teach that the *E. coli* strain is transformed with a nucleic acid encoding isopentenyl pyrophosphate isomerase; and 3) Wang teaches a nucleic acid encoding isopentenyl pyrophosphate isomerase. Applicants respectfully traverse the rejection.

Applicants respectfully assert that the rejection is in error and should be withdrawn, because (i) Takagi does not teach or suggest a process for forming IPP that involves "condensing two molecules of acetyl-CoA to acetoacetyl-CoA," which is required by each independent claim of the pending claims; (ii) Takagi does not provide any motivation to generate IPP in a genetically modified host cell, using a mevalonate pathway that involves condensing two molecules of acetyl-CoA to generate acetoacetyl-

CoA; and iii) the independent method claims do not include a step involving an isopentenyl pyrophosphate isomerase, and therefore Wang is not relevant to those claims;.

Takagi does not teach or suggest a process for generating IPP that involves condensing two molecules of acetyl-CoA.

Takagi discusses introducing into *E. coli* a construct that contains *Streptomyces* nucleotide sequences encoding mevalonate kinase, diphosphomevalonate decarboxylase, phosphomevalonate kinase, HMG-CoA synthase, and HMG-CoA reductase. To complete the mevalonate pathway as recited in instant claims 1 and 10, acetoacetyl-CoA must be generated. To generate acetoacetyl-CoA, Figure 1A of Takagi shows two enzymatic steps: 1) acetyl-CoA is carboxylated to generate malonyl-CoA; and 2) malonyl-CoA is acetylated to generate acetoacetyl-CoA. In contrast, instant claims 1 and 10 recite a mevalonate pathway that involves generating acetoacetyl-CoA by condensing two molecules of acetyl-CoA. Thus, Figure 1A of Takagi depicts a mevalonate pathway that is different from the mevalonate pathway recited in instant claims 1 and 10.

Takagi indicates that the acetoacetyl-CoA is formed via a reaction involving malonyl-CoA and not via condensing two molecules of acetyl-CoA to acetoacetyl-CoA, as required by each independent claim of the instant claims. In addition to Figure 1A of Takagi, which shows the malonyl-CoA reactant, Takagi describes the incorporation pattern of acetate labeled in the C1 position (see Figure 3 of Takagi) into the naturally produced *E. coli* isoprenoid ubiquinone. If two molecules of acetyl-CoA were to be condensed, the resulting ubiquinone would be equally labeled at the C-1 and C-3 positions. Because the isotopic abundance at the C3 position was nearly 3 times greater than that at the C1 position, Takagi concluded that the acetoacetyl-CoA was being produced via a malonyl-CoA intermediate. In this case, the C1 carbon in acetoacetate would come from the C1 carbon in malonyl-CoA, while the C3 carbon in acetoacetate would come from the C1 carbon in acetyl-CoA. Malonyl-CoA would have a lower enrichment at C-1 as compared to acetyl-CoA, thus resulting in an acetoacetyl-CoA with a higher enrichment at the C-3 position (derived from acetyl-CoA) than the C-1 position (derived from the malonyl-CoA).

The instant claims require that the IPP be made through a mevalonate pathway that generates acetoacetyl-CoA from two molecules of acetyl-CoA. Takagi neither discloses nor suggests such a pathway.

Takagi does not provide any motivation to generate IPP via a mevalonate pathway that involves condensing two molecules of acetyl-CoA.

Takagi states that *E. coli* possesses two sequences of acetoacetyl-CoA synthase, citing GenBank Accession Nos. P76461 and Q46936. GenBank Accession No. P76461 provides the amino acid sequence of acetoacetyl-CoA thiolase; and GenBank Accession No. Q46936 provides the amino acid sequence of transcriptional activator protein lysR. Transcriptional activator protein lysR is apparently not involved in the synthesis of acetoacetyl-CoA, and thus does not appear to be relevant to a discussion of acetoacetyl-CoA production. Takagi states that the role of the acetoacetyl-CoA thiolase depicted in GenBank Accession No. P76461 is "undefined." Takagi, page 4155, bridging paragraph, columns 1 and 2. Takagi goes on to conclude that the labeling data indicate that acetoacetyl-CoA is generated by the process depicted in Figure 1A of Takagi, i.e., a pathway involving carboxylation of acetyl-CoA to generate malonyl-CoA, and subsequent acetylation of malonyl-CoA to generate acetoacetyl-CoA.

Because Takagi indicates that the mevalonate pathway involves condensing acetyl-CoA and malonyl-CoA to generate acetoacetyl-CoA, and because Takagi indicates that the role of acetoacetyl-CoA thiolase is undefined, Takagi provides no motivation to generate IPP via a mevalonate pathway that involves condensing two molecules of acetyl-CoA.

Wang does not cure the deficiency of Takagi.

Wang does not cure the deficiency of Takagi. The isopentenyl pyrophosphate isomerase for which the Office Action cites Wang does not form acetoacetyl-CoA from acetyl-CoA. Instead, as disclosed in the specification at paragraph 0075, such enzymes are useful when "it is desired to retain isopentenyl pyrophosphate in the host microorganism for further biochemical processing, . . . the heterologous nucleic acid sequences . . . [can] include a DNA fragment coding for an enzyme capable of converting isopentenyl pyrophosphate to dimethylallyl pyrophosphate . . . . a suitable isomerase will catalyze the conversion of isopentenyl pyrophosphate into dimethylallyl pyrophosphate."

Because the combination of Takagi and Wang fails to teach or suggest all of the steps and elements of the claimed invention, the rejection of any of the claims of the instant application based on this combination is in error and should be withdrawn.

Claim 2 over Takagi in view of Wang and further in view of Balbas

The Office Action stated that Balbas teaches a method for integration of cloned DNA into the *E. coli* chromosome. The Office Action stated that it would have been obvious to modify the method of Takagi such that the nucleic acids are integrated into the *E. coli* strain. Applicants respectfully traverse the rejection.

As discussed above, the combination of Takagi and Wang fails to teach or suggest all of the steps and elements of the claimed invention. Balbas merely discusses a family of plasmids for chromosomal integration of cloned DNA into the *E. coli* genome. Balbas thus does not cure the deficiency of Takagi or Wang. Accordingly, Takagi and Wang, alone or in combination with Balbas, cannot render claim 2 obvious.

Claims 15-21 over Takagi in view of Wang and further in view of Fujisaki

The Office Action stated that Fujisaki teaches that isopentenyl pyrophosphate isomerase, farnesyl pyrophosphate synthetase, octaprenyl pyrophosphate synthetase, and undecanyl pyrophosphate synthetase are four enzymes in *E. coli* that in combination ensure the *in vivo* synthesis of long-chain isoprenoids in *E. coli*. The Office Action stated that it would have been obvious to modify the method of Takagi such hat the isoprenoid precursor is reacted with the enzymes taught by Fujisaki for the purpose of having a method that produces isoprenoids. Applicants respectfully traverse the rejection.

As discussed above, the combination of Takagi and Wang fails to teach or suggest all of the steps and elements of the claimed invention. Fujisaki, by merely discussing enzymes that are involved in *in vivo* synthesis of long-chain isoprenoids, does not cure the deficiency of Takagi and Wang. Accordingly, Takagi and Wang, alone or in combination with Fujisaki, cannot render claims 15-21 obvious.

Conclusion as to the rejections under 35 U.S.C.§103(a)

Applicants submit that the rejection of claims 1, 3, 4, 6-8, 10, 12-14, and 23 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

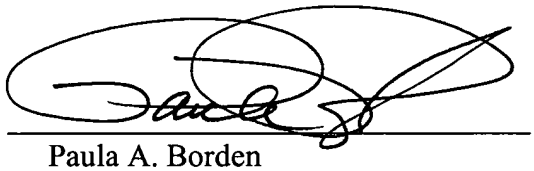
III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number BERK-036.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Oct. 6, 2005

By: 

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